THE CLINICAL FEATURES OF HUMAN PRION DISEASES:

Human Prion Diseases are divided into Sporadic, Genetic and Acquired (see The Different Types of Prion Disease). The commonest type of human prion disease is sporadic CJD.

The clinical features of each form of human prion disease are discussed below. All forms of prion disease are progressive and ultimately fatal. Currently, there are no treatments that have been shown to halt progression or to reverse the disease (see Treatment section). Prion diseases affect the brain and so lead to symptoms of brain dysfunction, including difficulties with movements, memory problems and dementia.

Please click on the following to find out more about:

Sporadic CJD | Variant CJD | Iatrogenic CJD | Genetic Prion Diseases | VPSPr

SPORADIC CJD

Sporadic CJD (sCJD) is predominantly a disease of late middle-age with a mean age at death in the late 60s. Cases with onset below the age of 50 are relatively rare, but do occur. The cause of sCJD is unknown.

Various early symptoms have been described, predating the main illness (including headache, tiredness, sleep or appetite disturbance and depression), but it is not clear whether these non-specific symptoms are really part of CJD in most cases. The presenting neurological symptoms usually reflect a disturbance in one relatively focal part of the brain but, in most cases, the disease develops rapidly to affect the brain in an increasingly global manner. Impairment of memory, cognition impairment and cerebellar ataxia (incoordination due to disease of the cerebellum) are common early features. Two particularly well-recognised but relatively rare presentations are the so-called Heidenhain and Brownell-Oppenheimer forms. In the first, the disease begins in the area of the brain that deals with vision and the affected individual complains of progressive visual disturbances and eventually blindness. There may be several weeks of purely visual problems before other features develop. In the second, there is a purely cerebellar disturbance with progressive unsteadiness and incoordination which again may progress for several weeks before other features are noted. Whatever the mode of onset, the subsequent clinical course, in most cases, is one of very rapid progression with deterioration being noticeable over even the course of a week. The rapidly evolving clinical picture always includes dementia (loss of memory and cognitive function), with ataxia and myoclonus (an involuntary jerking or twitching of muscles) being present in the majority of cases. Other features include impairment of voluntary movements and rigidity. It is common that walking and speech are lost after a relatively short period and the affected individual generally becomes bed-bound with no real awareness of, or response to, events around them. Epileptic seizures are relatively uncommon. The median duration of sCJD in the UK is 4 months and around 60% of cases have illness duration of less than 6 months. In 11% of cases, there is a relatively long duration of between 12 months and 2 years; durations of greater than 2 years are rare (4% of cases).

In a typical case, the invariably progressive, rapid clinical evolution and the short illness duration, readily distinguish sCJD from most other dementing illnesses. However, the differential diagnosis can be problematic, especially if there are atypical features and there are very rare cases with particularly unusual clinical profiles that make diagnosis in life very difficult.. If the initial symptoms remain focal for a while (such as visual or ataxia as described above), then other diagnoses will almost certainly be considered until the more general illness develops.

The diagnosis is reviewed in the investigations section.

IATROGENIC CJD

Iatrogenic CJD (iCJD) has resulted from neurosurgery (including the use of EEG depth electrodes), corneal grafting, human dura mater implants or exposure, and the use of human cadaveric growth hormone (hGH) and human pituitary gonadotrophin (hGNH). Iatrogenic CJD is very rare and most cases have resulted from hGH treatment or human dura mater grafts.

The clinical features depend somewhat on the route of infection.

> **hGH cases**, resulting from intra-muscular injection of infected material, generally present with a progressive cerebellar syndrome (increasing unsteadiness and incoordination) and other features including dementia tend to occur relatively late in the illness.
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> **Human dura mater cases**, resulting from infected material being placed relatively near to the CNS tend to present with a rapidly progressive dementia along with other neurological features and may be clinically indistinguishable from sporadic cases.

The principal investigation of iatrogenic disease must come from the history, in particular a history of treatment with cadaveric-derived hGH or an operation involving the use of a human dura mater graft.

The diagnosis is reviewed in the investigations section.

VARIANT CJD

In contrast to the age distribution of sCJD, the median age of onset in vCJD is 28 years (range 12-74). Whereas sCJD typically presents with rapidly progressive symptoms that are usually clearly neurological in nature, vCJD tends to present with behavioural or psychiatric symptoms and with a relatively slower progression. It may be difficult to determine that there is a neurological illness until some time has passed.

In an analysis of the first hundred cases of vCJD, psychiatric symptoms preceded neurological symptoms in 63% of cases and were found in combination with them in 22% of cases. In only 15% did neurological symptoms precede psychiatric symptoms. In the majority of cases, features of depression are present and many were given antidepressant treatment. Other features included anxiety, agitation, delusions and hallucinations. This presentation may result in the initial referral to psychiatry services

rather than neurological ones. Sensory symptoms in the limbs or elsewhere (persistent, unpleasant or frankly painful) affect nearly half the patients but these symptoms are relatively non-specific and such symptoms are relatively common in illnesses like depression. At some point other neurological features develop, with definite neurological abnormality developing at a mean of around 6 months from first symptoms, ataxia often being the most prominent problem. Certain involuntary movements may develop including chorea (fidgety movements) and dystonia (twisting, grimacing movements). Eventually, the clinical picture is one of a dementia with multiple neurological features including myoclonus. The illness duration is greater than that for sCJD, with a median of 14 months (range 6-114).

The differential diagnosis of a progressive neuropsychiatric disorder in relative youth is potentially a wide one and it may be difficult or impossible to make a diagnosis of vCJD in the early stages of illness.

The diagnosis is reviewed in the investigations section.

GENETIC PRION DISEASES

These diseases have an autosomal dominant pattern of inheritance (if an affected individual has a child, there is a 50% chance of the child inheriting the abnormality). However, for a variety of reasons, cases of genetic prion disease are identified where there is no obvious preceding family history.

Historically, these diseases have been divided into three main forms: genetic CJD, Gerstmann Sträussler Scheinker syndrome (GSS) and Fatal Familial Insomnia (FFI). They are all related to underying genetic mutations in the prion protein gene (*PRNP*) and could, therefore, be regarded as one group of diseases but they tend to be considered separately, having relatively distinct clinical and pathological features.

The clinical presentation varies with the underlying mutation and other factors. In some instances, the clinical picture is very like that of sCJD and the only definitive way of establishing the genetic nature of the illness is via the family history or genetic testing. The age at onset tends to be younger and the duration of illness longer than for sCJD. Some genetic cases have a particularly long duration (even of several years) and also atypical clinical profiles. GSS tends to present with progressive cerebellar ataxia. In FFI, sleep disturbances and other features predominate.

The presence of an abnormal mutation in the gene can be confirmed by a blood test. The diagnosis of genetic forms is dealt with in the investigations section.

VPSPr

Variably protease sensitive prionopathy (VPSPr) is a relatively newly described (in 2008) human prion diseases of unknown aetiology. Its precise relationship with other prion diseases is uncertain but no mutations have been found in the *PRNP* coding sequence and the patients have no (known) risk factors for iatrogenic CJD. The reported cases have clinico-pathological profiles and protein biochemical characteristics that differ from those seen in variat or sporadic CJD. The clinical features

are not yet fully characterised but the reported cases have been middle-aged to elderly with relatively longer disease durations than for sporadic CJD.